

## REMARKS

Claims 19, 23-36, 38-42, and 54-56 are pending with Claims 19, 27, and 33 being amended herein. Claim 27 has been amended to correct typographical and/or formatting errors. Claims 37 and 57 have been canceled. No new matter has been added with the amendments. Support for the amendments can be found in the claims as filed and in the specification, including at paragraphs [0012] and [0160].

### Rejections under 35 U.S.C. § 103(a)

Claims 19, 23-26, 28, 29, 30-36, 38, 39, and 40-42 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,040,194 (Chick et al.), in view of U.S. Patent No. 6,485,703 (Cote et al.) and U.S. Patent No. 6,377,721 (Walt et al.). The Examiner states, “Chick teaches an *in vivo* method and sensor for detecting an analyte in an individual qualitatively or quantitatively . . . . Chick is silent with regard to intracellular or extracellular concentrations of analytes measured . . . .” The Examiner then cites Walt et al. for teaching that the acetoxymethyl (AM) ester form of BCECF can be used as an intracellular fluorescent dye, wherein “increase in fluorescent intensity is indicative of the cell viability as a pH indicator” (col. 16, lines 48-61). Cote et al. teaches that it is important to monitor intracellular glucose in diabetic patients because, “the acute problems related to diabetes are correlated to intracellular glucose levels” (col. 24, lines 56-59). The Examiner states, “Cote provides the teaching that would motivate one of ordinary skill in the art to use the fluorophores (sic) known to be able to access intracellular information.”

The Examiner states, “One of ordinary skill in the art would have had a reasonable expectation of success because Walt describes how the acetoxymethyl (sic) ester form of BCECF passively enters the cell where, once inside the cell, the lipophilic blocking groups are cleaved by non-specific esterases resulting in an increase in fluorescent intensity.” Walt et al. teaches BCECF-AM as a cell membrane permeant pH indicator, and that “increase in fluorescent intensity is indicative of the cell viability” (col. 16, lines 48-61). However, a person of ordinary skill in the art would not have a reasonable expectation of success in trying to combine the teachings of Chick, Cote, and Walt to obtain the presently claimed invention. Independent Claims 19 and 33 currently recite, *inter alia*, penetrating a skin sensor composition into the epidermis, and correlating the change in the intracellular concentration of a metabolite or analyte (e.g., glucose) with *in vivo* blood concentration of the metabolite or analyte. Applicants note,

“There is a lag time for diffusion of glucose from the capillary fields of the dermis to the cells of the epidermis . . .” (specification, para. [0124]).

Chick et al. disclose a sensor that is “placed in communication with the body fluids (e.g., blood, plasma, or serum)” (col. 2, lines 36-37). Although the references cited by the Examiner may teach a cell membrane permeant, fluorescent pH indicator, and may teach the importance of monitoring intracellular glucose, they do not teach or suggest correlating the change in the intracellular concentration of a metabolite or analyte with the in vivo blood concentration of the metabolite or analyte, as presently claimed herein. Furthermore, there is no reasonable expectation that the combination of references cited by the Examiner will lead to success because none of the references take into account the lag time for diffusion of glucose from the capillary fields of the dermis to the cells of the epidermis. Therefore, even if intracellular fluorescent dyes are known in the art, and even if the importance of monitoring intracellular glucose has been taught, Applicants respectfully submit that, a person of ordinary skill in the art would not have a reasonable expectation of success in obtaining the invention as claimed.

Claims 27 and 37 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,040,194 (Chick et al.), in view of U.S. Patent No. 6,485,703 (Cote et al.) and U.S. Patent No. 6,377,721 (Walt et al.), and further in view of U.S. Patent No. 5,972,199 (Heller et al.). The Examiner acknowledges that the teachings of Chick, Cote, and Walt combined do not specifically disclose lactate as a metabolite to be measured. However, the Examiner argues that Heller teaches the importance of assaying lactate in certain fields such as medicine. Thus, the Examiner argues that one of ordinary skill in the art would have been motivated to use the methods of Chick to monitor levels of lactate in a patient. Additionally, the Examiner argues that one of ordinary skill in the art would have had a reasonable expectation of success because Chick teaches inorganic or organic ions generally as suitable analytes.

Heller et al. teaches “electrochemical sensors . . . measuring biochemicals in body fluids” (col. 1, lines 61-63). Applicants initially note that Claim 37 has been canceled. With respect to Claim 27, Applicants respectfully submit that although Heller discloses monitoring lactate concentrations in body fluids, Heller does not disclose the intracellular monitoring of lactate or other biochemicals. Furthermore, Heller does not teach or suggest correlating the change in the intracellular concentration of a metabolite or analyte with the in vivo blood concentration of the

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metabolite or analyte, as presently claimed herein. Therefore, Applicants respectfully submit that, a person of ordinary skill in the art would not have a reasonable expectation of success in obtaining the invention as claimed, as explained above.

Double Patenting Rejection

Claims 19, 23-42, and 54-57 were provisionally rejected on the ground of nonstatutory obviousness-type double patent as being unpatentable over claims 22-25, 31-50, 53 and 54 of copending Application No. 11/349,731. Without acquiescing to such rejection, a Terminal Disclaimer is being submitted with this Amendment to dispose of this rejection.

In view of the foregoing, it is respectfully asserted that Claims 19 and 33 are patentable. Furthermore, all claims depending directly or indirectly from Claims 19 and 33 are also patentable for at least the same reasons as discussed above for their respective independent claim, and also because each claim recites a novel and unobvious combination of elements.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following co-pending applications of the present application's assignee.

Serial Number	Title	Filed
11/349,731	NON-INVASIVE MEASUREMENT OF ANALYTES	Feb. 7, 2006

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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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AMEND

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